OCT 07 2002
PATENT & TRADEMARK OFFICE

#8

CLAIMS:

1. A composition for modulating bone regeneration, the composition comprising:

a matrix selected from the group consisting of glycolic acid, lactic acid, collagen, demineralized bone, or a combination thereof;

a first biologically active molecule comprising a fibronectin to facilitate osteoblast activity for promoting an increase in bone formation, the first biologically active molecule being attached to at least a portion of the matrix; and

a second biologically active molecule comprising a vitronectin selected for its ability to attract osteoclasts and produce an inhibiting effect on osteoclast activity to thereby promote a decrease in bone resorption, the second biologically active molecule being attached to at least a portion of the matrix substrate.

2. A composition as claimed in claim 1 wherein the fibronectin comprises an amino acid binding sequence that binds to the osteoblasts.

3. (Amended) A composition as claimed in claim 2 wherein the amino acid binding sequence is selected from one or more of the group consisting of:

RGD-Type (Arg-Gly-Asp) and
RGDS-Type (Arg-Gly-Asp-Ser), (SEQ ID NO: 23)
RGDC (Arg-Gly-Asp-Cys), (SEQ ID NO: 1)
RGDV (Arg-Gly-Asp-Val), (SEQ ID NO: 2)
RGES (Arg-Gly-Glu-Ser), (SEQ ID NO: 3)
GRGDS (Gly-Arg-Gly-Asp-Ser), (SEQ ID NO: 4)
GRADSP (Gly-Arg-Ala-Asp-Ser-Pro), (SEQ ID NO: 5)
KGDS (Lys-Gly-Asp-Ser), (SEQ ID NO: 6)

GRGDSP (Gly-Arg-Gly-Asp-Ser-Pro), (SEQ ID NO: 7)

GRGDTP (Gly-Arg-Gly-Asp-Thr-Pro), (SEQ ID NO: 8)

GRGES (Gly-Arg-Gly-Glu-Ser), (SEQ ID NO: 9)

GRGDSPC (Gly-Arg-Gly-Asp-Ser-Pro-Cys), (SEQ ID NO: 10)

GRGESP (Gly-Arg-Gly-Glu-Ser-Pro), (SEQ ID NO: 11)

SDGR (Ser-Asp-Gly-Arg), (SEQ ID NO: 12)

YRGDS (Tyr-Arg-Gly-Asp-Ser), (SEQ ID NO: 13)

GQQHHLGGAKQAGDV (Gly-Gln-Gln-His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val), (SEQ ID NO: 14)

GPR (Gly-Pro-Arg);

GHK-Type (Gly-His-Lys);

YIGSR-Type (Tyr-Ile-Gly-Ser-Arg); (SEQ ID NO: 15)

PDSGR (Pro-Asp-Ser-Gly-Arg); (SEQ ID NO: 16)

CDPGYIGSR (Cys-Asp-Pro-Gly-Tyr-Ile-Gly-Ser-Arg); (SEQ ID NO: 17)

laminin or laminin-fragment;

LCFR-Type (Leu-Cys-Phe-Arg); (SEQ ID NO: 18)

EIL-Type, EILDV (Glu-Ile-Leu-Asp-Val), (SEQ ID NO: 19)

EILDVPST (Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr), (SEQ ID NO: 20)

EILEVPST (Glu-Ile-Leu-Glu-Val-Pro-Ser-Thr); (SEQ ID NO: 21)

LDV-Type LDVPS (Leu-Asp-Val-Pro-Ser), (SEQ ID NO: 22)

LDV-NH_2 (Leu-Asp-Val-NH_2);

synthetic peptides containing the RGD, RGDS, GHK, LCFR or YIGSR sequence of amino acids;

osteonectin and SPARC (Secreted Protein Acidic and Rich in Cysteine);

osteopontin;

collagens, Type I and Type II;

von Willebrand Factor;

bone sialoprotein;

thrombospondin;

osteocalcin;

cytomodulin;

bone morphogenetic proteins (BMPs);

tenascins;

fibrinolysis inhibiting factor;

growth factors, Platelet Derived Growth Factors (PDGF), Insulin-Like Growth Factors (IGFs); and

antibodies to cell surface components, β-1; integrin antibody.

4. A composition as claimed in claim 1 wherein the vitronectin comprises an amino acid binding sequence that binds to the osteoclasts.

5. (Amended) A composition as claimed in claim 4 wherein the amino acid binding sequence is selected from one or more of the group consisting of:

RGD-Type (Arg-Gly-Asp) and

RGDS-Type (Arg-Gly-Asp-Ser), (SEQ ID NO: 23)

RGDC (Arg-Gly-Asp-Cys), (SEQ ID NO: 1)

RGDV (Arg-Gly-Asp-Val), (SEQ ID NO: 2)

RGES (Arg-Gly-Glu-Ser), (SEQ ID NO: 3)

GRGDS (Gly-Arg-Gly-Asp-Ser), (SEQ ID NO: 4)

GRADSP (Gly-Arg-Ala-Asp-Ser-Pro), (SEQ ID NO: 5)

KGDS (Lys-Gly-Asp-Ser), (SEQ ID NO: 6)

GRGDSP (Gly-Arg-Gly-Asp-Ser-Pro), (SEQ ID NO: 7)

GRGDTP (Gly-Arg-Gly-Asp-Thr-Pro), (SEQ ID NO: 8)

GRGES (Gly-Arg-Gly-Glu-Ser), (SEQ ID NO: 9)

GRGDSPC (Gly-Arg-Gly-Asp-Ser-Pro-Cys), (SEQ ID NO: 10)

GRGESP (Gly-Arg-Gly-Glu-Ser-Pro), (SEQ ID NO: 11)

SDGR (Ser-Asp-Gly-Arg), (SEQ ID NO: 12)

YRGDS (Tyr-Arg-Gly-Asp-Ser), (SEQ ID NO: 13)

GQQHHLGGAKQAGDV (Gly-Gln-Gln-His-His-Leu-Gly-Gly-Ala-Lys-Gln-Ala-Gly-Asp-Val), (SEQ ID NO: 14)

GPR (Gly-Pro-Arg);

GHK-Type (Gly-His-Lys);

YIGSR-Type (Tyr-Ile-Gly-Ser-Arg); (SEQ ID NO: 15)

PDSGR (Pro-Asp-Ser-Gly-Arg); (SEQ ID NO: 16)

CDPGYIGSR (Cys-Asp-Pro-Gly-Tyr-Ile-Gly-Ser-Arg); (SEQ ID NO: 17)

laminin or laminin-fragment;

LCFR-Type (Leu-Cys-Phe-Arg); (SEQ ID NO: 18)

EIL-Type, EILDV (Glu-Ile-Leu-Asp-Val), (SEQ ID NO: 19)

EILDVPST (Glu-Ile-Leu-Asp-Val-Pro-Ser-Thr), (SEQ ID NO: 20)

EILEVPST (Glu-Ile-Leu-Glu-Val-Pro-Ser-Thr); (SEQ ID NO: 21)

LDV-Type LDVPS (Leu-Asp-Val-Pro-Ser), (SEQ ID NO: 22)

LDV-NH_2 (Leu-Asp-Val-NH_2);

synthetic peptides containing the RGD, RGDS, GHK, LCFR or YIGSR sequence of amino acids;

osteonectin and SPARC (Secreted Protein Acidic and Rich in Cysteine);

osteopontin;

collagens, Type I and Type II;

von Willebrand Factor;

bone sialoprotein;

thrombospondin;

osteocalcin;

cytomodulin;

bone morphogenetic proteins (BMPs);

tenascins;

fibrinolysis inhibiting factor;

growth factors, Platelet Derived Growth Factors (PDGF), Insulin-Like Growth Factors (IGFs); and

antibodies to cell surface components, β-1; integrin antibody.

6. A composition as claimed in claim 1 further comprising spacer molecules between the matrix and the first and/or second biologically active molecules.

7. A composition as claimed in claim 6 wherein the spacer molecules are selected from homo-bifunctional or hetero-bifunctional cross-linking agents.

8. A composition as claimed in claim 6 wherein the spacer molecules comprise polymeric spacers.

9. A composition as claimed in claim 8 wherein the polymeric spacers are selected from the group consisting of: polyethoxylates, polyethylene glycol, polysorbitols, and combinations thereof.

10. A method of making a composition for modulating bone regeneration comprising:

selecting a matrix from the group consisting of glycolic acid, lactic acid, collagen, demineralized bone, or a combination thereof;

attaching a first biologically active molecule comprising a fibronectin to facilitate osteoblast activity for promoting an increase in bone formation to at least a portion of the matrix; and

attaching a second biologically active molecule comprising a vitronectin selected for its ability to attract osteoclasts and produce an inhibiting effect on osteoclast activity to thereby